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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/381,032	12/17/1999	ANDREAS BERGMANN	PM263260	3417

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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 01/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/381,032	BERGMANN ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-25 and 27-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-25, and 27-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 23-25, and 27-33 are pending.

2. In view of the amendment filed 10/28/04, the following rejections remain.

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 23-25, and 27-33 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Vitti *et al* (of record, Acta Med Austriaca 23(1-2): 52-6, 1996; PTO 892) in view of Harlow et al (of record, in Antibodies A Laboratory Manual, Cold Spring Harbor Laboratory 1988, pages 556, 564-591), and Nicholson e*t al* (of record, J Mol Endocrinol 16(2): 159-70, 1996; PTO 892) or Morgenthaler *et al* (of record, J Clin Endocrinol Metab 81(2):700-6, Feb 1996, PTO 892).

Vitti *et al* teach a method for the determination of TSH receptor autoantibodies where the autoantibodies mimic TSH (thyroid stimulating antibody) found in Grave's disease (See page 53, column 1, in particular). The reference method comprises purified CHO cell expressing the recombinant human thyrotropin receptor that has been transfected with cDNA encoding the human thyrotropin receptor (See abstract, in particular), follows by immobilized the TSH receptor on the host cell to a solid phase such as petri dishes (See page 53, column 2, Cell culture, in particular), or immobilized porcine TSH-receptor to a plate (TRAK assay, page 53, col. 2, TSH-

receptor antibodies (TRAb), reacting a liquid sample such as IgG prepared from sera of patients with Graves's disease, separating the a reacted solid phase from the liquid biological sample by centrifugation, washing the reacted solid phase, incubating the solid phase with radiolabeled ^{125} iodine bovine TSH to either the bovine TSH receptor or the human TSH receptor. The TSH-receptor antibodies (TRAb) are measured by a commercial radioreceptor assay based on inhibition of binding of ^{125}iodine bovine TSH to porcine TSH-receptor or solubilized human TSH receptor on CHO cells using commercially available assay (TRAK assay, page 53, TSH-receptor Antibodies (TRAb), in particular). Vitti *et al* teach most autoantibodies to TSH receptor are measured by their ability to inhibit the binding of radiolabeled TSH to its receptor present in solubilized thyroid membrane preparations (See page 53, column 1, in particular).

The claimed invention differs from the teachings of the references only in that the method wherein the recombinant human TSH receptor is immobilized to a solid support by a selective monoclonal antibody that recognizes only conformational epitopes of the human TSH receptor and is obtained by immunizing an animal with a DNA plasmid construct encoding the human TSH receptor instead of a cell expressing the human TSH receptor or the bovine TSH receptor.

The claimed invention as recited in claim 25 differs from the teachings of the reference only in that the method wherein the solid phase is formed by the walls of the test tubes, which are precoated with an animal-specific antibody for binding the selective antibody against the receptor.

Harlow *et al* teach various immunoassays for detecting and quantitating any antibodies in a sample or test solution wherein the reference antigen (the TSH receptor in this case) is immobilized to a solid support such as test tube, or multi-well plate using an antibody that binds specifically to the antigen. The test solution or dilution of the test solution (with buffer) containing an unknown amount of antibody such as the auto-TSH receptor antibody is added. Antibodies in the test solution are allowed to bind to the immobilized antigen in the present of radiolabeled TSH and unbound antibodies are removed by washing. The presence of the bound antibodies is detected by direct counting using a gamma counter based on competitive binding of radiolabeled TSH to the TSH receptor. Harlow *et al* teach the advantages of antibody sandwich immunoassays are: it is rapid and easy, quantitative, and sensitive with detection limit about 0.01 to 0.1 ng (See page 584, in particular).

Nicholson *et al* teach various human TSH receptor antibodies such as A7, A8, A9, A10 and A11 that bind to various epitopes localized to various regions on the human TSH receptor

(See entire document, page 168, in particular). The reference monoclonal antibodies such as A10 and A11 recognize the conformational epitopes of the human TSH receptor since the antibodies bind only to acetone fixation and not by PLP fixation of thyroid section, suggesting the reference antibodies recognize the conformational epitope of the human TSH receptor (See abstract, in particular). Nicholson *et al* teach further teach that the reference human TSH receptor is produced by various cDNA constructs in insect cells as well as in Escherichia coli (See page 160, in particular). The reference antibodies are produced by immunizing mice with the human TSH receptors produced by the cDNA constructs (See production of mAbs, in particular). Nicholson *et al* teach the reference antibodies are useful for radiolabeled TSH to porcine membranes in a radioreceptor assay (See Abstract, in particular).

Morgenthaler *et al* teach antibodies such as A7, A9 and A10 that bind specifically to the recombinant human TSH receptor for detecting TSH receptor autoantibodies in Graves' disease (See entire document; abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the porcine TSH receptor in the commercial TRAK assay as taught by the Vitti et al for the recombinant human TSH receptor immobilized by monoclonal antibody that recognized by the conformational epitopes of human TSH receptor as taught by Nicholson *et al* or Morgenthaler *et al* instead of immunbolized the recombinant human TSH receptor using the CHO cells as taught by Vitti et al for a method of determining TSH receptor autoantibodies in human serum from patient with Grave's disease. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Harlow *et al* teach that the advantages of antibody sandwich immunoassays are: it is rapid, easy, quantitative, and sensitive with a detection limit about 0.01 to 0.1 ng (See page 584, in particular). Nicholson *et al* teach the reference antibodies are useful for radiolabeled TSH to porcine membranes in a radioreceptor assay (See Abstract, in particular). Morgenthaler *et al* teach antibodies such as A7, A9 and A10 to recombinant human TSH receptor are useful for detecting TSH receptor autoantibodies in Graves' disease (See entire document; abstract, in particular). Vitti et al teach human TSH receptor has been cloned and are suitable for detection of TSH autoantibodies (See page 53, col. 1, in particular). The recitation of monoclonal antibody that recognizes only conformational epitopes of the human TSH receptor obtained by immunizing

an animal with a DNA plasmid construct encoding the human TSH receptor is irrelevant to the claimed method because the antibody is merely use to immobilized the human TSH receptor. Any monoclonal antibody that binds to human TSH receptor is useful for the claimed method as taught by Harlow, Nicholson and Morgenthaler *et al.* Further, the monoclonal antibodies such as A10 and A11 as taught by Nicholson e*t al* or Morgenthaler *et al* have the same property as the monoclonal antibody in the claimed method that recognize only conformational epitopes of the human TSH receptor and the reference antibodies are useful for determining TSH receptor autoantibodies from patients with Graves' disease as taught by Nicholson and Morgenthaler *et al.* Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibodies are different from the antibodies in the claimed method. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977).

Applicants' arguments filed 10/28/04 have been fully considered but are not found persuasive.

Applicants' position is that (1) claims 23-24, 27, 31 and 33 have been amended to recite "functional recombinant human TSH receptor" is immunobilized to a solid support. (2) Vitti et al. does not discuss an affinity-purified immobilized functional recombinant human TSH receptor immobilized to a solid support by a selective monoclonal antibody that recognized only conformational epitopes of human TSH receptor. Indeed, the TRAK assay referred to by the Examiner as having immobilized porcine TSH-receptor a plate, is still a TSH receptor in solubilized form as seen on page 55 right hand column of Vitti et al which states "the TSH receptor is contained in a solubilized membrane preparation." This inadequacy is not addressed by any of the secondary references. (3) with regard to '363 patent, the examiner refers to col. 7, lines 8-63 and col. 8 lines 3-11 outlining competitive binding assays employing radiolabeled TSH and TSH receptor. A TSH receptor protein which undergoes such purification steps as discussed in col. 7 does not retain its functionality (if the purified recombinant TSH receptor was a functional TSH receptor at all). The discussion at col 8 at best suggests only a use of the assay, but hardly enables a skilled artisan to develop a useful solid phase assay for the detection of the claimed antibodies in serum or plasma samples of patients. It is noted that conventional assays, at the time of the '363 patent, used solubilized porcine TSH receptors almost exclusively. Therefore, the discussion could not fairly be cited as evidence of a suggestion of the solid phase techniques of the present invention.

In contrast to applicant's argument that TSH receptor protein which undergoes such purification steps as discussed in col. 7 of the'363 patent does not retain its functionality, applicant's/inventor's assertions are not found persuasive in view of the lack of objective evidence. In fact, the specification of instant application on page 23 discloses that "Cells which contained the expressed rather in their cell membrane were digested to obtain a solubilized rather preparation, as described in more detail in S. Costagliola et al., J. Clin. Endocrinol. Metab. 752 1540-1544 (1992).

In response to applicant's argument that conventional assays, at the time of the '363 patent, used solubilized porcine TSH receptors almost exclusively and could not fairly be cited as evidence of a suggestion of the solid phase techniques of the present invention, the claimed invention is merely an improvement over the prior art as disclosed on page 11 of the specification. The claimed assay uses purified immobilized human TSH receptor instead of solubilized porcine TSH receptor to determine TSH receptor autoantibodies in human. It would have been obvious one of ordinary skill in the art at the time the invention was made to use human TSH receptor to measure human TSH receptor autoantibodies.

Vitti *et al* teach a method for the determination of TSH receptor autoantibodies where the autoantibodies mimic TSH (thyroid stimulating antibody) found in Grave's disease in human (See page 53, column 1, in particular). The reference method comprises purified CHO cell expressing the recombinant human thyrotropin receptor that has been transfected with cDNA encoding the human thyrotropin receptor (See abstract, in particular). The recombinant hTSH receptor is immobilized by host cell to a solid phase such as Petri dishes instead of monoclonal antibody that recognizes only conformational epitopes of the human TSH receptor and is obtained by immunizing an animal with a DNA plasmid construct encoding the human TSH receptor instead of a cell expressing the human TSH receptor or the bovine TSH receptor.

The claimed invention as recited in claim 25 differs from the teachings of the reference only in that the method wherein the solid phase is formed by the walls of the test tubes, which are precoated with an animal-specific antibody for binding the selective antibody against the receptor.

The claimed invention differs from the teachings of the references only in that the method wherein the recombinant human TSH receptor is immobilized to a solid support by a selective monoclonal antibody that recognizes only conformational epitopes of the human TSH receptor

and is obtained by immunizing an animal with a DNA plasmid construct encoding the human TSH receptor instead of a cell expressing the human TSH receptor or the bovine TSH receptor.

The claimed invention as recited in claim 25 differs from the teachings of the reference only in that the method wherein the solid phase is formed by the walls of the test tubes, which are precoated with an animal-specific antibody for binding the selective antibody against the receptor.

Harlow *et al* teach various immunoassays for detecting and quantitating any antibodies in a sample or test solution wherein the reference antigen (the TSH receptor in this case) is immobilized to a solid support such as test tube, or multi-well plate using an antibody that binds specifically to the antigen. The test solution or dilution of the test solution (with buffer) containing an unknown amount of antibody such as the auto-TSH receptor antibody is added. Antibodies in the test solution are allowed to bind to the immobilized antigen in the present of radiolabeled TSH and unbound antibodies are removed by washing. The presence of the bound antibodies is detected by direct counting using a gamma counter based on competitive binding of radiolabeled TSH to the TSH receptor. Harlow *et al* teach the advantages of antibody sandwich immunoassays are: it is rapid and easy, quantitative, and sensitive with detection limit about 0.01 to 0.1 ng (See page 584, in particular).

Nicholson *et al* teach various human TSH receptor antibodies such as A7, A8, A9, A10 and A11 that bind to various epitopes localized to various regions on the human TSH receptor (See entire document, page 168, in particular). The reference monoclonal antibodies such as A10 and A11 recognize the conformational epitopes of the human TSH receptor since the antibodies bind only to acetone fixation and not by PLP fixation of thyroid section, suggesting the reference antibodies recognize the conformational epitope of the human TSH receptor (See abstract, in particular). Nicholson *et al* teach further teach that the reference human TSH receptor is produced by various cDNA constructs in insect cells as well as in Escherichia coli (See page 160, in particular). The reference antibodies are produced by immunizing mice with the human TSH receptors produced by the cDNA constructs (See production of mAbs, in particular). Nicholson *et al* teach the reference antibodies are useful for radiolabeled TSH to porcine membranes in a radioreceptor assay (See Abstract, in particular).

Morgenthaler *et al* teach antibodies such as A7, A9 and A10 that bind specifically to the recombinant human TSH receptor for detecting TSH receptor autoantibodies in Graves' disease (See entire document; abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the porcine TSH receptor in the commercial TRAK assay as taught by the Vitti et al for the recombinant human TSH receptor immobilized by monoclonal antibody that recognized by the conformational epitopes of human TSH receptor as taught by Nicholson *et al* or Morgenthaler *et al* instead of immunbolized the recombinant human TSH receptor using the CHO cells as taught by Vitti et al for a method of determining TSH receptor autoantibodies in human serum from patient with Grave's disease. It would have been obvious to one of ordinary skill in the art at the time the invention was made to use functional recombinant human TSH receptor to measure human TSH receptor autoantibodies given that recombinant human TSH receptor is readily available as taught by Vitti *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Harlow *et al* teach that the advantages of antibody sandwich immunoassays are: it is rapid, easy, quantitative, and sensitive with a detection limit about 0.01 to 0.1 ng (See page 584, in particular). Nicholson *et al* teach the reference antibodies are useful for radiolabeled TSH to porcine membranes in a radioreceptor assay (See Abstract, in particular). Morgenthaler *et al* teach antibodies such as A7, A9 and A10 to recombinant human TSH receptor are useful for detecting TSH receptor autoantibodies in Graves' disease (See entire document; abstract, in particular). Vitti et al teach human TSH receptor has been cloned and are suitable for detection of TSH autoantibodies (See page 53, col. 1, in particular). The recitation of monoclonal antibody that recognizes only conformational epitopes of the human TSH receptor obtained by immunizing an animal with a DNA plasmid construct encoding the human TSH receptor is irrelevant to the claimed method because the antibody is merely use to immobilized the human TSH receptor. Any monoclonal antibody that binds to human TSH receptor is useful for the claimed method as taught by Harlow, Nicholson and Morgenthaler *et al.* Further, the monoclonal antibodies such as A10 and A11 as taught by Nicholson *et al* or Morgenthaler *et al* have the same property as the monoclonal antibody in the claimed method that recognize only conformational epitopes of the human TSH receptor and the reference antibodies are useful for determining TSH receptor autoantibodies from patients with Graves' disease as taught by Nicholson and Morgenthaler *et al.* Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art

antibodies are different from the antibodies in the claimed method. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977).

6. Claims 23-25, 27-33 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,614,363 (of record, March 1997, PTO 892) in view of Vitti *et al* (of record, Acta Med Austriaca 23(1-2): 52-6, 1996; PTO 892), Harlow et al (of record, in Antibodies A Laboratory Manual, Cold Spring Harbor Laboratory 1988, pages 556, 564-591), and Nicholson e*t al* (of record, J Mol Endocrinol 16(2): 159-70, 1996; PTO 892) or Morgenthaler *et al* (of record, J Clin Endocrinol Metab 81(2):700-6, Feb 1996, PTO 892).

The '363 patent teaches recombinant human TSH receptor for detection of auto-antibodies found in Graves' patients in the form of a competitive binding assay employing radiolabeled TSH and TSH receptor (See column 7, lines 8-63, column 8, lines 3-11, claim 9 of '363, in particular). The reference purified recombinant human TSH receptor is immobilized on a support matrix (See column 9, line 24-38, in particular). The immobilized human TSH receptor is incubated with excess TSH that has been tagged with a radioactive or fluorescent label, long enough for the binding reaction to come to equilibrium. Unbound TSH is removed by a washing step and the receptor is incubated with the test sample. Once the second binding step has come to equilibrium, the immobilized receptor is washed again. The amount of tagged TSH displace by TSH in the test sample than serves as a measure of TSH present in the sample (See claim 9 of '363 patent, col. 9, lines 24-38, in particular).

The claimed invention differs from the teachings of the reference only in that the method wherein the recombinant human TSH receptor is immobilized to a solid support by a selective monoclonal antibody that recognizes only conformational epitopes of the human TSH receptor and is obtained by immunizing an animal with a DNA plasmid construct encoding the human TSH receptor instead of a cell expressing the human TSH receptor or the bovine TSH receptor.

The claimed invention as recited in claim 25 differs from the teachings of the reference only in that the method wherein the solid phase is formed by the walls of the test tubes, which are precoated with an animal-specific antibody for binding the selective antibody against the receptor.

Vitti *et al* teach a method for the determination of TSH receptor autoantibodies where the autoantibodies mimic TSH (thyroid stimulating antibody) found in Grave's disease (See page 53, column 1, in particular). The reference method comprises purified CHO cell expressing the

recombinant human thyrotropin receptor that has been transfected with cDNA encoding the human thyrotropin receptor (See abstract, in particular), follows by immobilized the TSH receptor on the host cell to a solid phase such as petri dishes (See page 53, column 2, Cell culture, in particular), or immobilized porcine TSH-receptor to a plate (TRAK assay, page 53, col. 2, TSH-receptor antibodies (TRAb), reacting a liquid sample such as IgG prepared from sera of patients with Graves's disease, separating the a reacted solid phase from the liquid biological sample by centrifugation, washing the reacted solid phase, incubating the solid phase with radiolabeled ^{125} iodine bovine TSH to either the bovine TSH receptor or the human TSH receptor. The TSH-receptor antibodies (TRAb) are measured by a commercial radioreceptor assay based on inhibition of binding of ^{125}iodine bovine TSH to porcine TSH-receptor or solubilized human TSH receptor on CHO cells using commercially available assay (TRAK assay, page 53, TSH-receptor Antibodies (TRAb), in particular). Vitti *et al* teach most autoantibodies to TSH receptor are measured by their ability to inhibit the binding of radiolabeled TSH to its receptor present in solubilized thyroid membrane preparations (See page 53, column 1, in particular).

Harlow *et al* teach various immunoassays for detecting and quantitating any antibodies in a sample or test solution wherein the reference antigen (the TSH receptor in this case) is immobilized to a solid support such as test tube, or multi-well plate using an antibody that binds specifically to the antigen. The test solution or dilution of the test solution (with buffer) containing an unknown amount of antibody such as the auto-TSH receptor antibody is added. Antibodies in the test solution are allowed to bind to the immobilized antigen in the present of radiolabeled TSH and unbound antibodies are removed by washing. The presence of the bound antibodies is detected by direct counting using a gamma counter based on competitive binding of radiolabeled TSH to the TSH receptor. Harlow *et al* teach the advantages of antibody sandwich immunoassays are: it is rapid and easy, quantitative, and sensitive with detection limit about 0.01 to 0.1 ng (See page 584, in particular).

Nicholson *et al* teach various human TSH receptor antibodies such as A7, A8, A9, A10 and A11 that bind to various epitopes localized to various regions on the human TSH receptor (See entire document, page 168, in particular). The reference monoclonal antibodies such as A10 and A11 recognize the conformational epitopes of the human TSH receptor since the antibodies bind only to acetone fixation and not by PLP fixation of thyroid section, suggesting the reference antibodies recognize the conformational epitopes of the human TSH receptor (See abstract, in particular). Nicholson *et al* teach further teach that the reference human TSH receptor is

produced by various cDNA constructs in insect cells as well as in Escherichia coli (See page 160, in particular). The reference antibodies are produced by immunizing mice with the human TSH receptors produced by the cDNA constructs (See production of mobs, in particular). Nicholson *et al* teach the reference antibodies are useful for radiolabeled TSH to porcine membranes in a radioreceptor assay (See Abstract, in particular).

Morgenthaler *et al* teach antibodies such as A7, A9 and A10 that bind specifically to the recombinant human TSH receptor for detecting TSH receptor autoantibodies in Graves' disease (See entire document; abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to immobilized the recombinant human TSH receptor as taught by the '363 patent using any monoclonal antibody that binds specifically to the human TSH receptor as taught by Nicholson *et al* or Morgenthaler *et al* for a method for determining TSH receptor autoantibodies as taught by the '363 patent, Harlow *et al*, and Vitti *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Harlow *et al* teach that the advantages of antibody sandwich immunoassays are: it is rapid, easy, quantitative, and sensitive with a detection limit about 0.01 to 0.1 ng (See page 584, in particular). Nicholson *et al* teach the reference antibodies are useful for radiolabeled TSH to porcine membranes in a radioreceptor assay (See Abstract, in particular). Morgenthaler *et al* teach antibodies such as A7, A9 and A10 to recombinant human TSH receptor are useful for detecting TSH receptor autoantibodies in Graves' disease (See entire document; abstract, in particular). The '363 patent teaches recombinant human TSH receptor for detection of auto-antibodies found in Graves' patients in the form of a competitive binding assay employing radiolabeled TSH and TSH receptor (See column 7, lines 8-63, column 8, lines 3-11, claim 9 of '363, in particular). The recitation of monoclonal antibody that recognizes only conformational epitopes of the human TSH receptor obtained by immunizing an animal with a DNA plasmid construct encoding the human TSH receptor is irrelevant to the claimed method because the antibody is merely use to immobilized the human TSH receptor. Any monoclonal antibody that binds to human TSH receptor is useful for the claimed method as taught by Harlow, Nicholson and Morgenthaler *et al*. Further, the monoclonal antibodies such as A10 and A11 as taught by Nicholson *et al* or Morgenthaler *et al* have the same property as the monoclonal antibody in the

claimed method that recognize only conformational epitopes of the human TSH receptor and the reference antibodies are useful for determining TSH receptor autoantibodies from patients with Graves' disease as taught by Nicholson and Morgenthaler *et al.* Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibodies are different from the antibodies in the claimed method. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977).

7. No claim is allowed.

8. **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

10. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
January 21, 2005

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